KEITH REIMER, M.D.

1946-2002

Keith Arnold Reimer, M.D., Ph.D., Professor of Pathology at Duke University Medical School, internationally recognized cardiovascular scientist, pathologist, and teacher, died on March 15, 2002 of metastatic renal cell carcinoma at the age of 56. Keith began his career in experimental pathology studying ischemic injury of the kidney, however he quickly shifted his focus to myocardial ischemic injury, the field in which he went on to make his major scientific contributions. After completing the MD/PhD program at Northwestern University in Chicago, Keith joined the faculty at Duke University in 1975 as Assistant Professor of Pathology. Early in his career, working in collaboration with Dr. Robert B. Jennings, he published landmark studies describing and characterizing the "wavefront phenomenon" of myocardial ischemic cell death. These studies, published in two papers (Circulation 56: 786-794, 1977; and Laboratory Investigation 40: 633-644, 1979), have been cited more than 1000 times. During the early 1980s, Keith developed methods to measure baseline predictors of infarct size, such as area at risk and collateral flow, that have become the standard for generating reliable and reproducible data to test cardioprotective interventions. The effort to discover cardioprotective interventions led to one of Keith's most notable achievements – the description of one of the strongest and most reproducible interventions for reducing infarct size: ischemic preconditioning. Numerous investigators and laboratories have worked to better understand this remarkably effective intervention, and the ever-expanding number of studies on ischemic preconditioning, in a wide variety of tissues, have consistently confirmed the original observation that brief periods of ischemia and reperfusion are not detrimental, but are actually markedly protective. The original article describing the phenomenon of ischemic preconditioning, "Preconditioning with ischemia: a delay of lethal cell injury in ischemic myocardium" (Circulation 74: 1124-1136, 1986) has been cited more than 3700 times (the most cited paper in *Circulation*).

Keith was an active member of the ISHR since 1976, and was elected a Councilor of the American Section in 1979, serving until 1985. He was a finalist for the Richard Bing Young Investigator Award of the ISHR in 1980. Keith served as Secretary of the American Section from 1985-1994, and as a member of the Council of the International Society from 1989-1995. In 1997, he became President-Elect of the American Section and was the sitting President of the American Section, as well as a member of the International ISHR Council, when he died.

About the Award…

Each year, the International Council selects a speaker to deliver the Keith Reimer Distinguished Lecture at the World Congress or at the annual section meeting of one of the three largest ISHR Sections. The purpose of this lecture is to honor the memory of Dr. Reimer and to recognize his contributions to cardiovascular research. The topic of the lecture must be in the field of ischemia, coronary hemodynamics, cardiac metabolism, or contractile mechanisms. The speaker receives a plaque and $1,000 honorarium in addition to travel expenses.

This award is funded by a generous contribution from Chugai-Pharmaceutical Co.

ISHR

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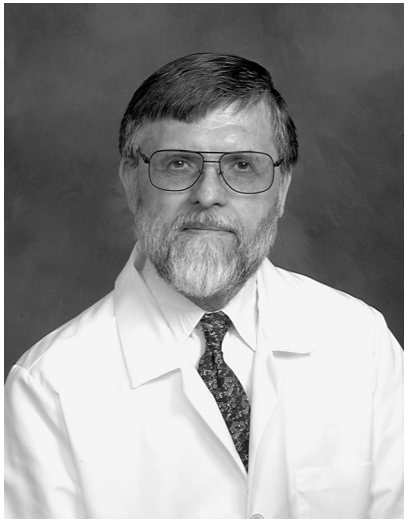
THE KEITH REIMER DISTINGUISHED LECTURE 2014



Keith Reimer, M.D. 1946–2002

Honored Speaker

Dr. Fabio Di Lisa

"Ca^{2+}, ROS and mitochondria: orchestrating cardiac pathophysiology"

Fabio Di Lisa, M.D.

2014 Honored Speaker
Nagoya, Japan

Fabio Di Lisa is Professor of Biochemistry at the University of Padova, Italy. He received his MD degree and Board Certification in Cardiology at the Catholic University in Rome. Attracted by basic research more than clinical activities he joined Roberto Ferrari at the University of Parma to start experimental studies in the field of ischemia and reperfusion focusing on cardiac metabolism and mitochondrial function. This latter topic prompted his transfer to the University of Padova that was, and still is, the most advanced center for mitochondrial research in Italy. In 1987, accepting a NATO fellowship he worked in the laboratory of Loran Bieber at the Department of Biochemistry at Michigan State University focusing on the role carnitine in mitochondrial metabolism. He was then a Visiting Associate (1991-92) in the laboratory of Richard Hansford within the NIA-NIH Unit led by Edward Lakatta in Baltimore.

Prof. Di Lisa became a CNR Researcher in 1984 and then he was appointed Associate Professor and Full Professor of biochemistry in 1992 and 2002, respectively. In 1992 he started an independent laboratory in the Department of Biochemistry. Since 2007 he is affiliated with the Department of Biomedical Sciences. Besides an intense teaching schedule he has worked on numerous tasks coordinating the organization and the evaluation of scientific research both within the University of Padova and in National Councils.

Prof. Di Lisa was President of the European Section of the International Society for Heart Research (ES-ISHR) from 2005 to 2008. During this term, in 2007 he organized the ES -ISHR meeting in Padova and co-organized the ISHR World Congress in Bologna. He was elected Fellow of the ISHR in 2007, and at present, he is a member of the ISHR International Council. Regarding other Societies, he has been part of the Congress Programme Committee of the European Society of Cardiology for various terms (2005-2014), and he served on the Scientific Council of the Society for Heart and Vascular Metabolism organizing the annual meeting in Padova in 2009. Prof. Di Lisa is a member of the Editorial Board of the *Journal of Biological Chemistry* and journals in the cardiovascular field, such as the *Journal of Molecular and Cellular Cardiology*, *Cardiovascular Research* and *Basic Research in Cardiology*.

Prof. Di Lisa has provided significant contributions elucidating the role of mitochondrial dysfunction in cardiac diseases. He started his scientific activity characterizing mitochondrial alterations in ischemia/reperfusion and substrate utilization, especially highlighting the role of carnitine. Considering that findings obtained in isolated mitochondria might not always reflect the behavior of these organelles *in situ*, in the early nineties in Baltimore he started investigating mitochondrial function in isolated cardiomyocytes. He added the assessment of mitochondrial membrane potential to the measurement of intracellular and mitochondrial Ca^{2+} developed in Lakatta's laboratory to define patterns of mitochondrial dysfunction during anoxia and reoxygenation. In particular, he found that the mitochondrial membrane potential is maintained during anoxia using ATP produced by glycolysis, so that mitochondria changes from ATP producers into avid ATP utilizers. He also demonstrated that myocardial failure could be the result of a reduced Ca^{2+} uptake rather than Ca^{2+} overload. An interest in Ca^{2+} homeostasis triggered Di Lisa's interest in proteolysis of myofibrillar proteins. He demonstrated that calpain-catalyzed cleavage of troponin I and T is modulated by their phosphorylation, and their fragments are linked by transglutaminase as a result of Ca2+ overload occurring upon post-ischemic reperfusion. Myofibrillar proteins were also found to represent binding sites for cytosolic proteins redistributing during ischemia because of acidosis and ATP depletion.

A long-standing friendship with Paolo Bernardi was the driving force to start a fruitful collaboration on the mitochondrial permeability transition pore (PTP) that is still ongoing. By developing methods to study the PTP in isolated cells and intact hearts Prof. Di Lisa characterized the occurrence of transient and prolonged openings demonstrating that the latter modality is involved in cell death. In addition, PTP opening was causally related to NAD depletion and loss of viability induced by reperfusion. Derangements of mitochondria and myofibrillar proteins paved the way for studies on oxidative alterations and ROS formation. After highlighting tropomyosin as a target of oxidative stress in reperfused hearts, in collaboration with Gerd Heusch and Rainer Schulz Prof. Di Lisa demonstrated that the oxidation of myofibrillar proteins correlates linearly with contractile impairment. This relationship that applies to various experimental models and human heart failure has been extended to muscular dystrophy. Concomitantly, bridging the gap between contractile proteins and mitochondria he provided evidence that reactive oxygen species are produced mostly within mitochondria, and especially by p66Shc and mono amine oxidases (MAO). Moving from ischemia/reperfusion injury to myocardial failure, in collaboration with Nazareno Paolocci and David Kass, MAO was shown to contribute to maladaptive remodeling highlighting also the potential therapeutic efficacy of MAO inhibition. This concept has been further documented in muscular dystrophy.

At present, the interest in PTP, ROS formation and Ca^{2+} homeostasis has been directed towards diabetic cardiomyopathy while maintaining the traditional focus on ischemia/reperfusion and mechanisms of cell death.

Previous Award Winners…

Karin Sipido, MD, PhD: 2013
Metin Avkiran, DSc, PhD: 2012
Charles Murry, MD, PhD: 2011
Richard Moss, PhD: 2010
Elizabeth Murphy, PhD : 2009
David Eisner, PhD: 2008
Eduardo Marbán, MD: 2007
Garrett Gross, PhD: 2006
Masao Endoh, MD, PhD: 2005
R. John Solaro, PhD: 2004
Gerd Heusch, MD, PhD: 2003
Roberto Bolli, MD: 2002